Diabetes and Kidney: How can we support SGLT2i/MRA revolution?

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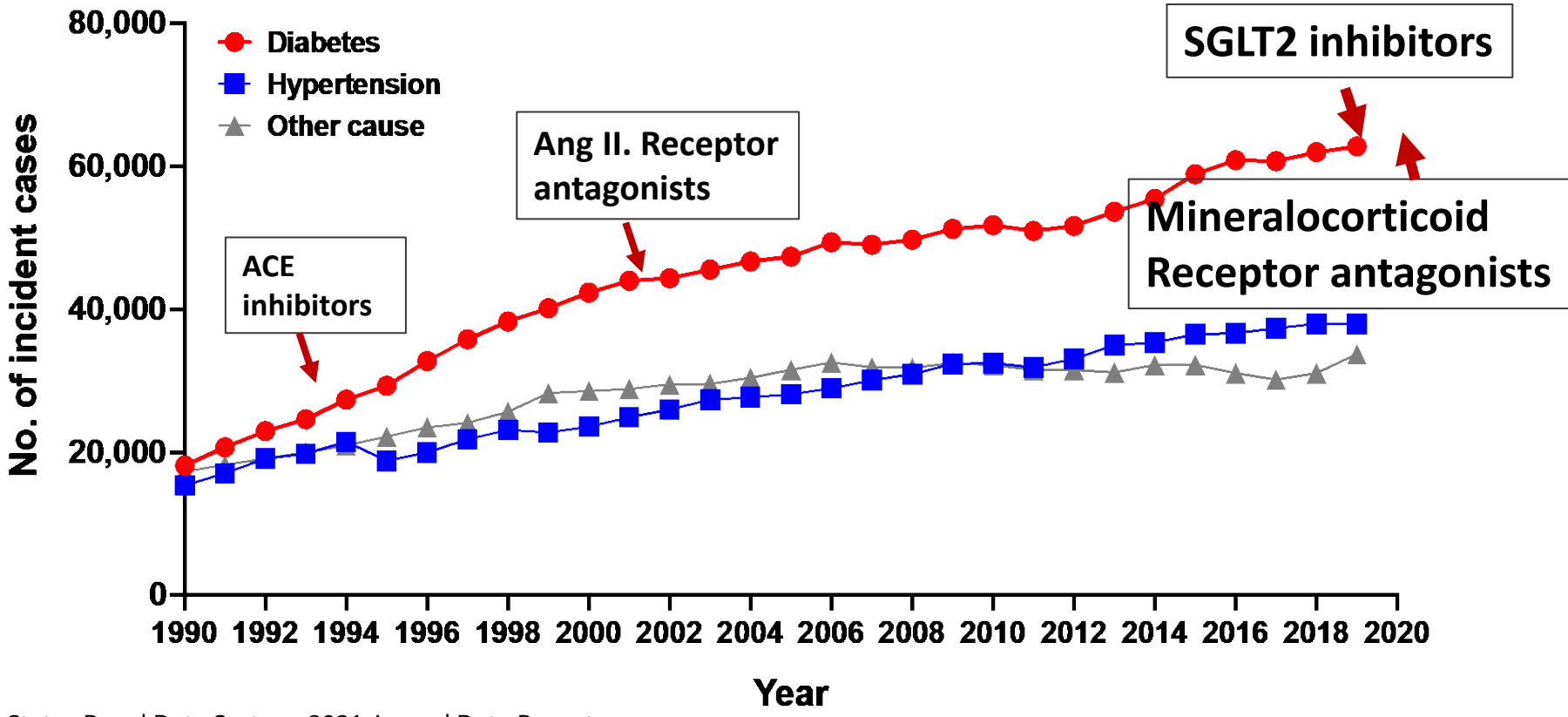
HARVARD MEDICAL SCHOOL

Joslin Diabetes

Number of incident cases of ESKD, by primary cause — United States, 1990–2019



United States Renal Data System, 2021 Annual Data Report

Comparison of effect of Finerenone treatment on risk of Kidney Outcomes with effect of SGLT2 inhibitor treatment.

Agarwal R et al. Neph.Dial Transplant 2022

	FIDELIO-DKD Trial		CREDENCE trial	
Kidney outcomes	**Placebo N=2328 Rate/100py**	**Finerenone N=2291 Rate/100py**	**Placebo N=2199 Rate/100py**	**SGLT2 inhibitor N=2202 Rate/100py**
Kidney Failure	**2.82**	**2.28**	**2.94**	**2.09**
Sustain decrease in GFR >57%	**3.72**	**2.42**	**3.38**	**2.07**
All Kidney end-points	**4.41**	**3.06**	**4.04**	**2.70**

Comparison of effect of Finerenone treatment on risk of Kidney Outcomes with effect of SGLT2 inhibitor treatment.

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Kidney Failure	**2.82**	20%	**2.28**	**2.94**	29%	**2.09**
Sustain decrease in GFR >57%	**3.72**	35%	**2.42**	**3.38**	39%	**2.07**
All Kidney end-points	**4.41**	31%	**3.06**	**4.04**	33%	**2.70**

Finerenone Treatment and Risk of Kidney Failure according to SGLT2 inhibitor treatment. The FIDELITY Analysis

Rossing et al. Diabetes Care 2022

	Numbers		Rates	
	Placebo	Finerenone	Placebo	Finerenone
Treatment in Sub-groups at baseline	*Events/ patients*	*Events / patients*	*Rate per 100 py*	*Rate per 100/py*
No SGLT2	448/6,061	351/6,081	2.64	2.06
With SGLT2 -inhibitor	17/439	9/438	1.37	0.70

Preliminary results suggest additive effects of Finerenone and SGLT2 inhibitors.

The superiority of dual therapy is currently examined in the CONFIDENCE trial.

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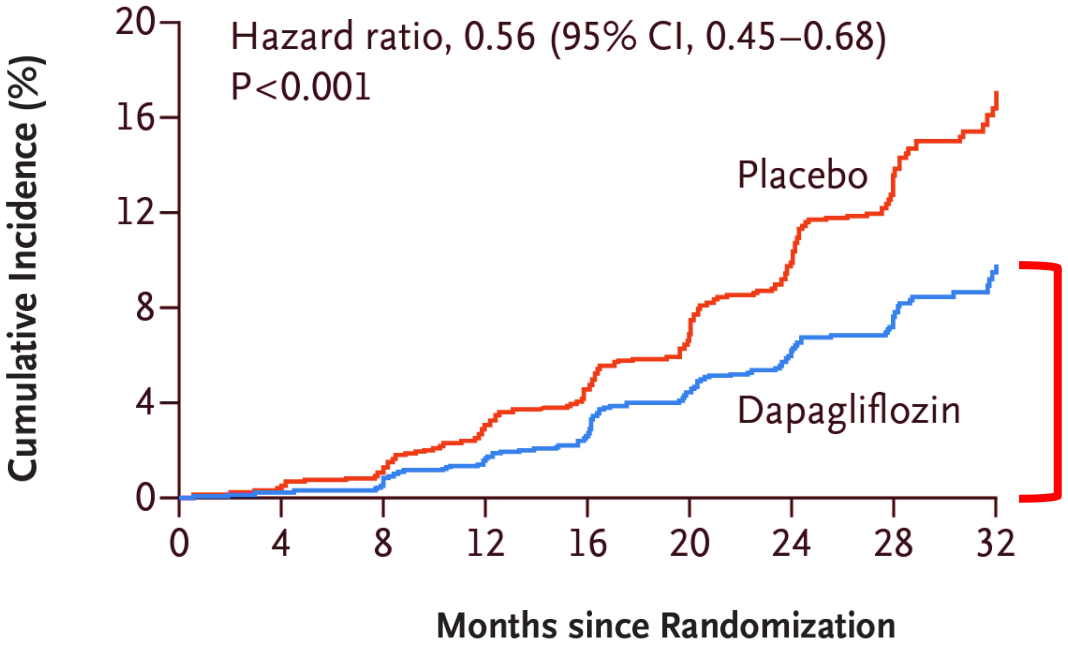
Doctors would like to know who should be treated with which drug and how to monitors whether drugs are working – Precision Medicine

Cumulative incidence of Kidney Composite End-points in DAPA-CKD trial

Heerspink H JL et al NEJM 2020



Despite treatment 2/3 of patients Are progressing

No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

Our research to support SGLT2i/MRA revolution

1. Proteomics study to search for circulating proteins to predict who is at risk of ESKD to identify patients to be treated

2. Development of Joslin Kidney Panel (JKP) of 21 informative proteins to predict which of reno-protective therapies should be prescribed (precision medicine)

3. Search for new therapeutic targets to develop new reno-protective drugs, example of NBL1 (Neuroblastoma Suppressor Tumorigenecity 1)

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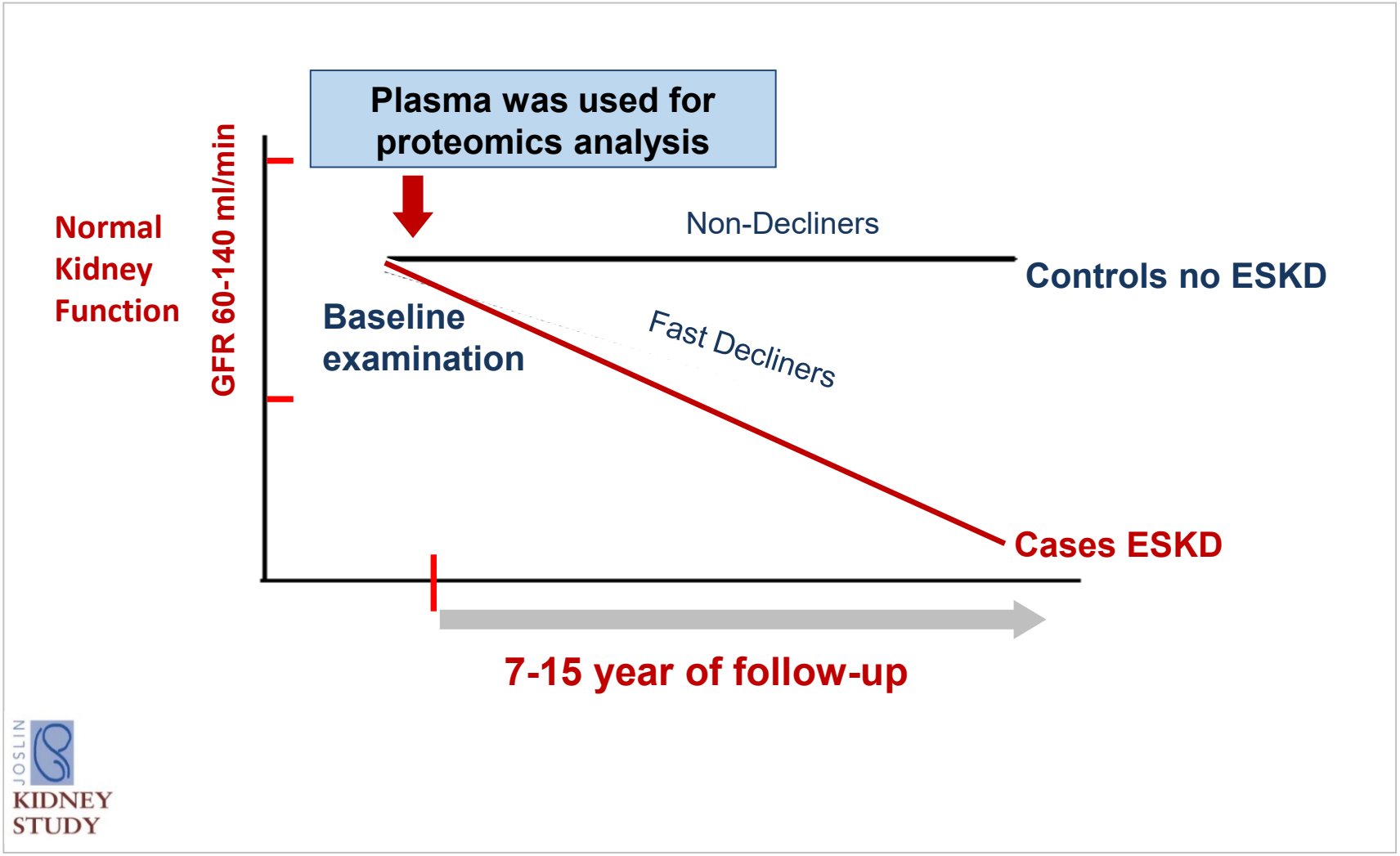
Study Design:
Four cohorts of patients with T1D & T2D followed for 7-15 years were used for proteomics study



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Characteristics of Study COHORTS (n=754) used in our proteomics research

	Late DKD		Early DKD	
Characteristics	Joslin T1D Discovery cohort	Joslin T2D Replication cohort	Joslin T1D Validation cohort	Pima T2D Validation cohort
	N=239	N=136	N=243	N=154
At Baseline				
Age (years)	44	60	39	46
Duration of DM (years)	30	16	26	16
HbA_{1c} (%)	8.6	7.5	9.0	9.4
SBP (mmHg)	136	139	131	125
ACR (mg/g)	793	555	579	55
GFR (ml/min)	42 ± 10	49 ± 11	97 ± 21	150 ± 47
During Follow-up:				
New cases of ESKD within 10 years (n/%)	127 (53%)	43 (32%)	50 (21%)	37 (24%)

Baseline plasma was used for SOMAscan proteomics analyses. 1129 plasma proteins were analyzed.

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SOMAscan related PUBLICATIONS

1) **Monika Niewczas**, et al. A Signature of Circulating Inflammatory Proteins and Development of ESRD in Diabetes. ***Nature Med. 2019: 25(5):805-813***

2) **Eiichiro Satake,** et al. Comprehensive Search for Novel Circulating miRNAs and Axon Guidance Pathway Proteins Associated with Risk of ESKD in Diabetes. ***J Am Soc Nephrol. 2021: 32(9):2331-51***

3) **Zaipul Md Dom,** et al. Circulating Proteins Protect against Kidney Decline and Progression to ESKD in Diabetes: Results of Global Proteomics Profiling. ***Science Transl Med. 2021; 13(600):eabd2699***

4) **Hiroki Kobayashi**, *et al.* Neuroblastoma suppressor of tumorigenicity 1 is a circulating protein associated with progression to end-stage kidney disease in diabetes. ***Sci Transl Med. 2022 Aug 10;14(657):eabj2109.***

5) **Hiroki Kobayashi,** et al. Results of untargeted analysis using the SOMAscan proteomics platform indicates novel associations of circulating proteins with risk of progression to kidney failure in diabetes. ***Kidney Int. 2022 Aug;102(2):370-381.***

In total, out of 1129 proteins, 34 were robustly associated with progression to ESKD and the findings were replicated & validated in all 4 cohorts.

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List of 34 circulating proteins associated with Early and Late progressive kidney function decline leading to ESKD identified by SOMAscan platform

	Category	Protein name	Function
17 KRIS proteins	Inflamatory	TNFRSF1A	TNF receptor
	Inflamatory	TNFRSF1B	TNF receptor
	Inflamatory	TNFRSF19	TNF receptor
	Inflamatory	TNFRSF21	TNF receptor
	Inflamatory	TNFRSF27	TNF receptor
	Inflamatory	TNFSF15	TNF Ligand
	Inflamatory	RELT	TNF receptor
	Inflamatory	CCL14	Ligand
	Inflamatory	CCL15	Ligand
	Inflamatory	CD55	Immunoregulatory receptor
	Inflamatory	CD300C	Immunoregulatory receptor
	Inflamatory	CSF1	Ligand
	Inflamatory	HAVCR2	Immunoregulatory receptor
	Inflamatory	IL1R1	Immunoregulatory receptor
	Inflamatory	IL15RA	Immunoregulatory receptor
	Inflamatory	IL18R1	Immunoregulatory receptor
	Inflamatory	IL17F	Ligand
2 AGP proteins	Axon guidance	EFNA4	Ligand
	Axon guidance	EPHA2	Other receptor
1 TGF-B signaling proteins	TGF-B related	NBL1	Inhibitor
3 Protective proteins	Protective	ANGPT1	Ligand
	Protective	FGF20	Ligand
	Protective	TNFSF12	Ligand
11 Other proteins	Others	COL18A1	Inhibitor
	Others	DLL1	Ligand
	Others	ESAM	Others
	Others	FABP3	Others
	Others	KLK8	Enzyme
	Others	LAYN	Immunoregulatory receptor
	Others	MAPK11	Enzyme
	Others	MATN2	Others
	Others	NRXN1	Others
	Others	ROR1	Other receptor
	Others	RTN4R	Other receptor

Joslin Kidney Panel

Contains 21 proteins

Will be used to identify patients at risk of ESKD

Will be used to select reno-protective Rx (precision medicine)

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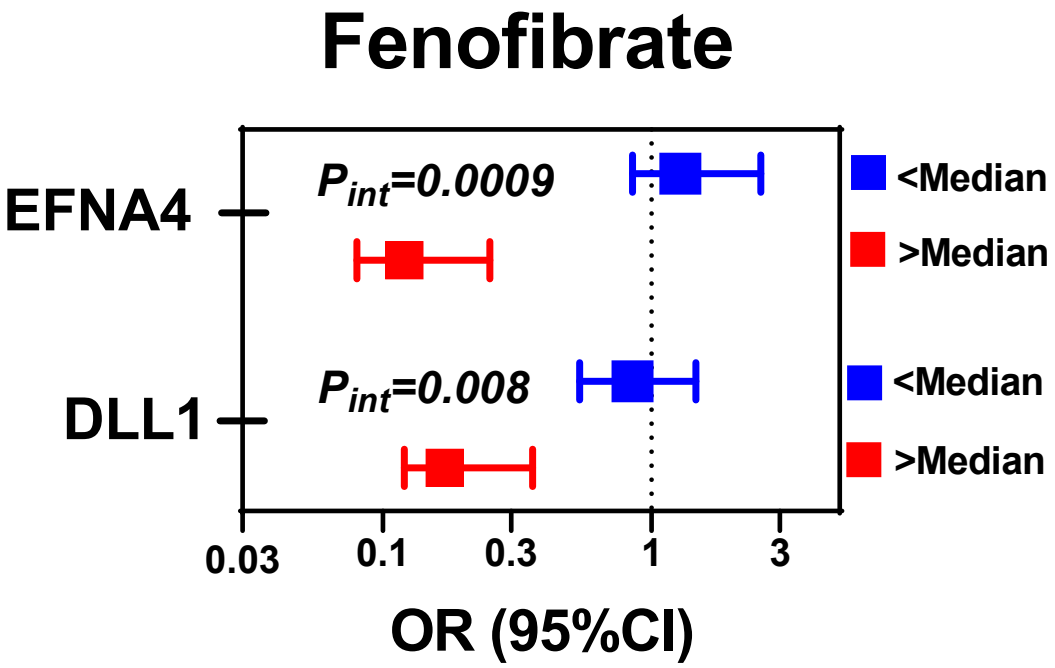
21 Proteins on Joslin Kidney Panel

Protein	Protein
Inflammation	*Fibrosis*
TNF-R1A	DLL1
TNF-R1B	LAYN
TNF-R3	PI3
TNF-R6B	PVRL4
TNF-R7	SYND1
TNF-R10A	WFDC2
TNF-R4	*Axon-guidance*
TNF-R19L	EFNA4
TNF-R27	EPHA2
CD160	GFRa1
IL-1RT1	*Other*
	KIM1

ACCORD Clinical Trial
Out of 21 proteins on Joslin Kidney Panel,
two circulating proteins measured at baseline predicted beneficial effect of Fenofibrate during 6 year follow-up
Example of precision medicine in nephrology



Patients with T2D and high levels of two circulating proteins EFNA4 and DLL1 should be treated with Fenofibrat.
We search for biomarkers for treatment with SGLT2i and Finerenone.

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Our Contribution to SGLT2i/MRA revolution

1. Search for circulating proteins to predict who is at risk of ESKD to identify patients to be treated

2. Development of Joslin Kidney Panel (JKP) of 21 informative proteins to predict which of reno-protective therapies should be prescribed (precision medicine)

3. Search for new therapeutic targets to develop new reno-protective drugs, example of NBL1 (Neuroblastoma Suppressor Tumorigenecity 1)

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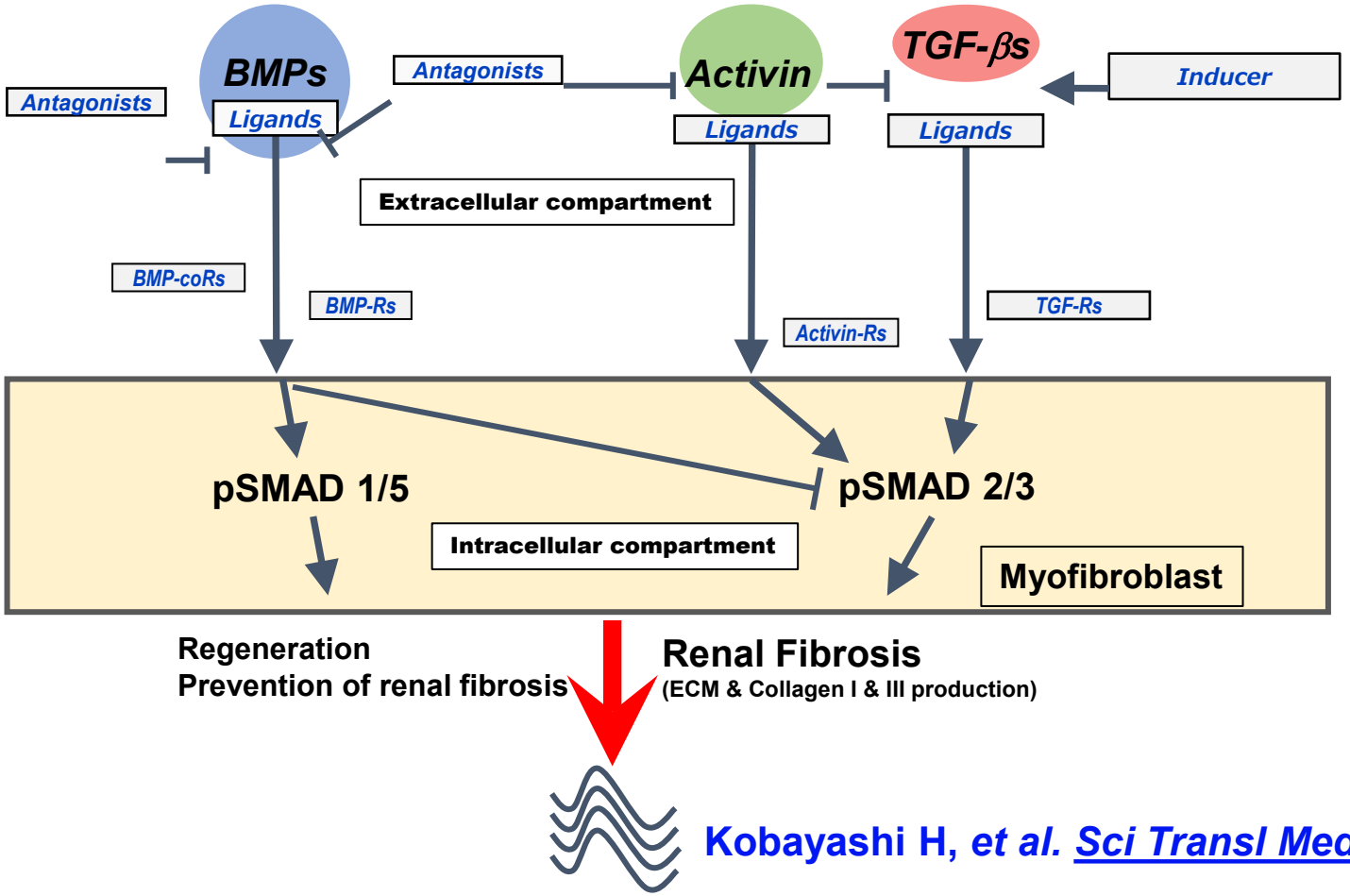
Hiroki Kobayashi

Candidate Pathway Approach

Circulating proteins involved in TGF-β signaling



Kobayashi H, *et al.* *Sci Transl Med.* 2022

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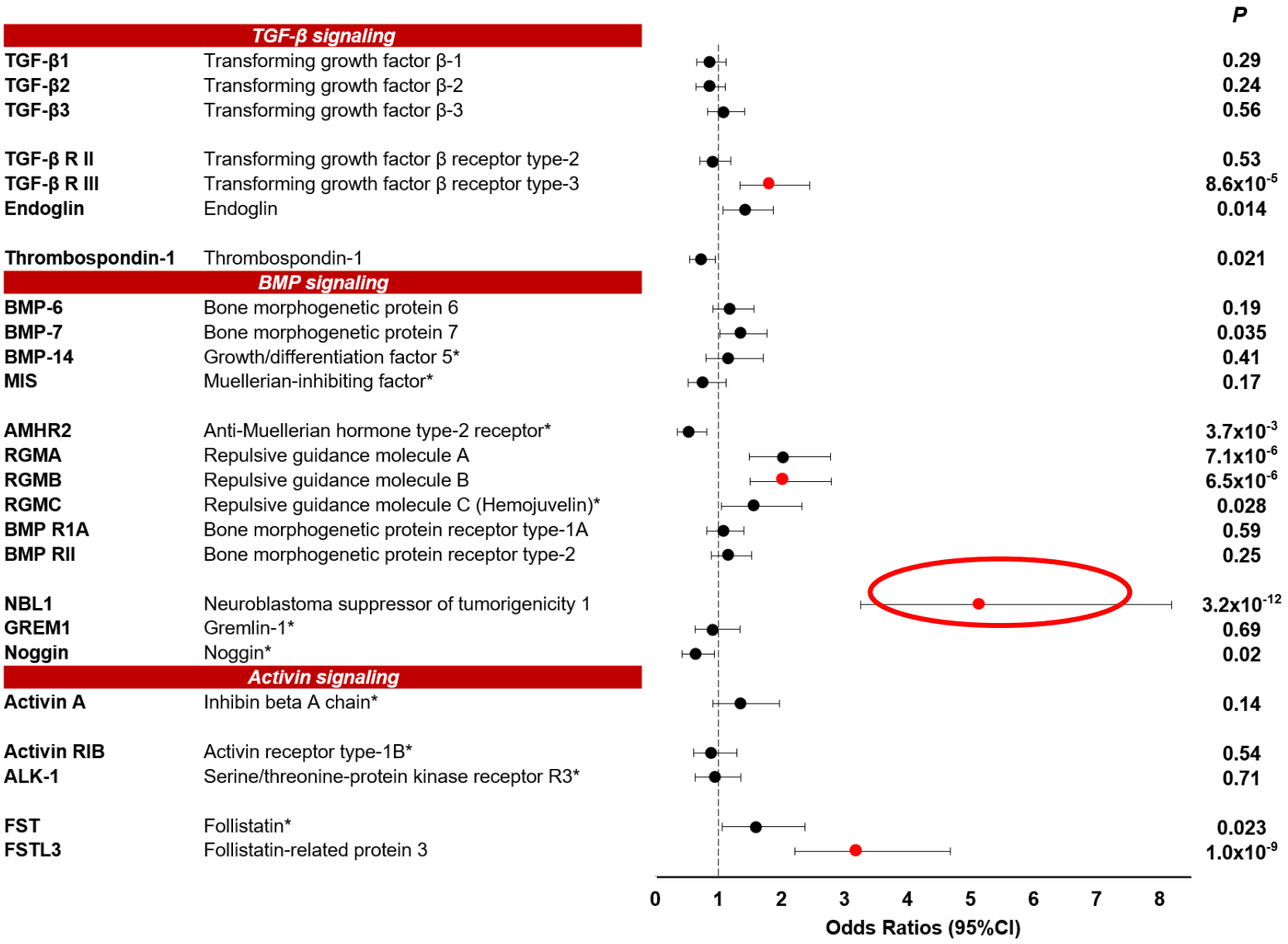
25 TGF-β related proteins were measured by SOMAscan
Results of association with 10-year risk of ESKD



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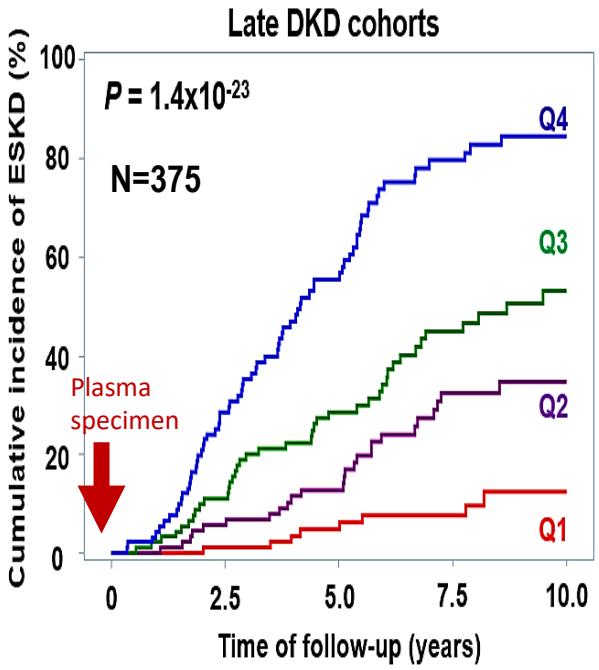
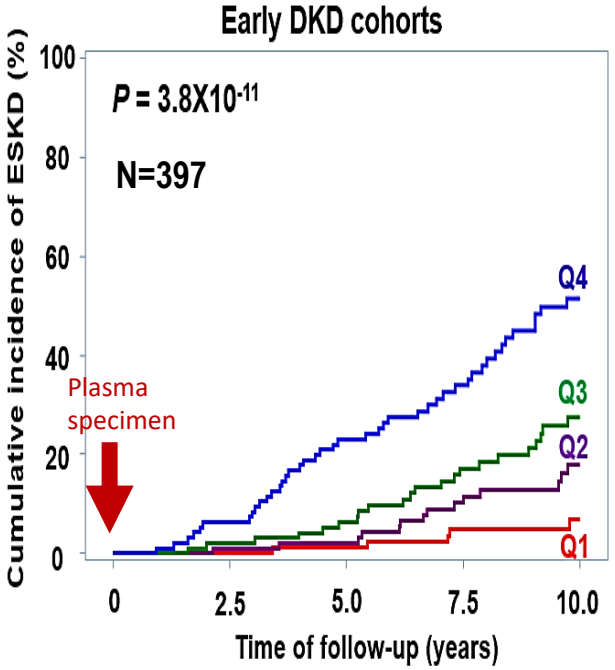
Cumulative risk of ESKD according to baseline level of circulating NBL1 in 4 study cohorts during 10-year follow-up.





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Circulating NBL1 may damage directly the Kidney

Correlation between circulating NBL1 and structural lesions in kidney biopsies: PIMA Indians Kidney Study

		Circulating proteins			
		NBL1	TNFR1	BMP7	TGF-β1
Category of lesions	Measured lesion	Spearman Correlation Coefficients			
		r	*r*	*r*	*r*
Podocyte damage	Podocyte number per glomerulus (N)	-0.26**	-0.08	-0.06	-0.01
	Fractional volume of podocyte cells per glomerulus	-0.34***	-0.16	0.17	-0.11
Mesangial expansion	Mesangial fractional volume (%)	0.49***	0.31**	-0.07	-0.04
Glomerular filtration barrier disruption	Percent fenestrated endothelium (%)	-0.52***	-0.52***	-0.08	0.01
	Glomerular filtration surface density (μ^2/μ^3)	-0.48***	-0.28**	-0.02	-0.01
	Glomerular basement membrane width (nm)	0.41***	0.27**	0.06	-0.03
Kidney fibrosis	Cortical interstitial fractional volume (%)	0.39***	0.25*	-0.03	0.13
	Global glomerular sclerosis (%)	0.17	0.12	0.07	-0.08

In collaboration with Looker H & Nelson R

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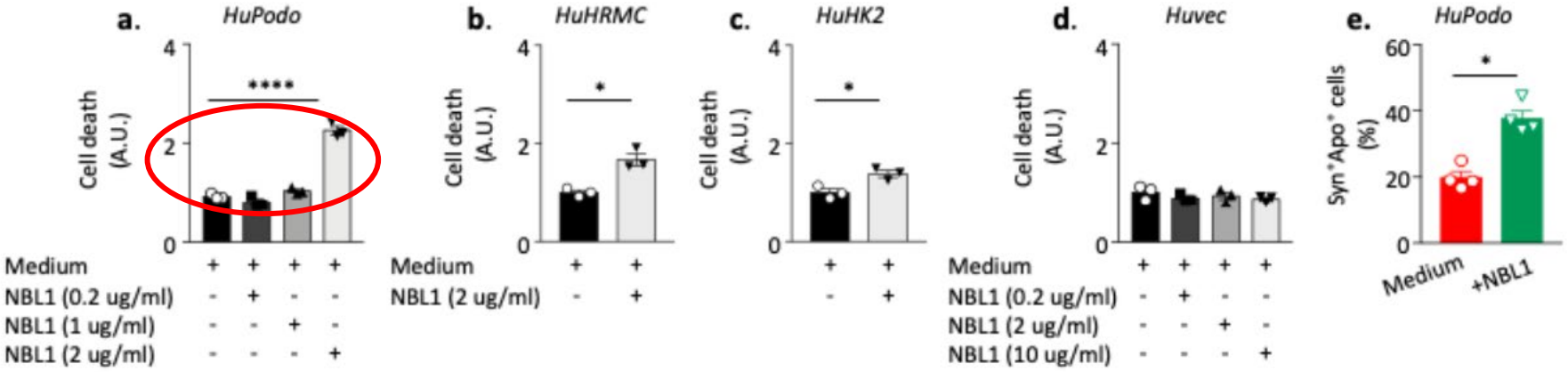
Mechanism through which NBL1 may damage the Kidney

Effect of NBL1 exposure on apoptosis in kidney cells



In collaboration with: Drs. Francesca D'Addio, Adriana Petrazzuolo and Prof. Paolo Fiorina
Università di Milano and Endocrinology Division ASST Sacco-FBF, Milan, Italy;

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About NBL1 (Neuroblastoma Suppressor of Tumorigenicity 1)

- NBL1 was discovered as suppressor of tumorigenicity in neuroblastoma cell line.
- NBL1 is a secreted protein, binds to circulating Bone Morphogenic Proteins (BMPs) and inhibits SMAD 1/5 proteins.
- As the consequence high circulating levels of NBL1 may promote TGF-β signaling and fibrosis of kidney
- NBL1 may be toxic for kidney cells.

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Summary of our contributions to SGLTi/MRA Revolution

1. We found 34 circulating proteins associated with risk of ESKD

2. We developed the Joslin Kidney Panel (JKP) of 21 informative proteins to predict which of reno-protective therapies: SGLTi or MRA or both should be prescribed (precision medicine)

3. We found NBL1 (Neuroblastoma Suppressor Tumorigenecity 1), a new therapeutic target to develop new reno-protective drug.

With Prof. Fiorina we are working on findings such a drug.

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Acknowledgement

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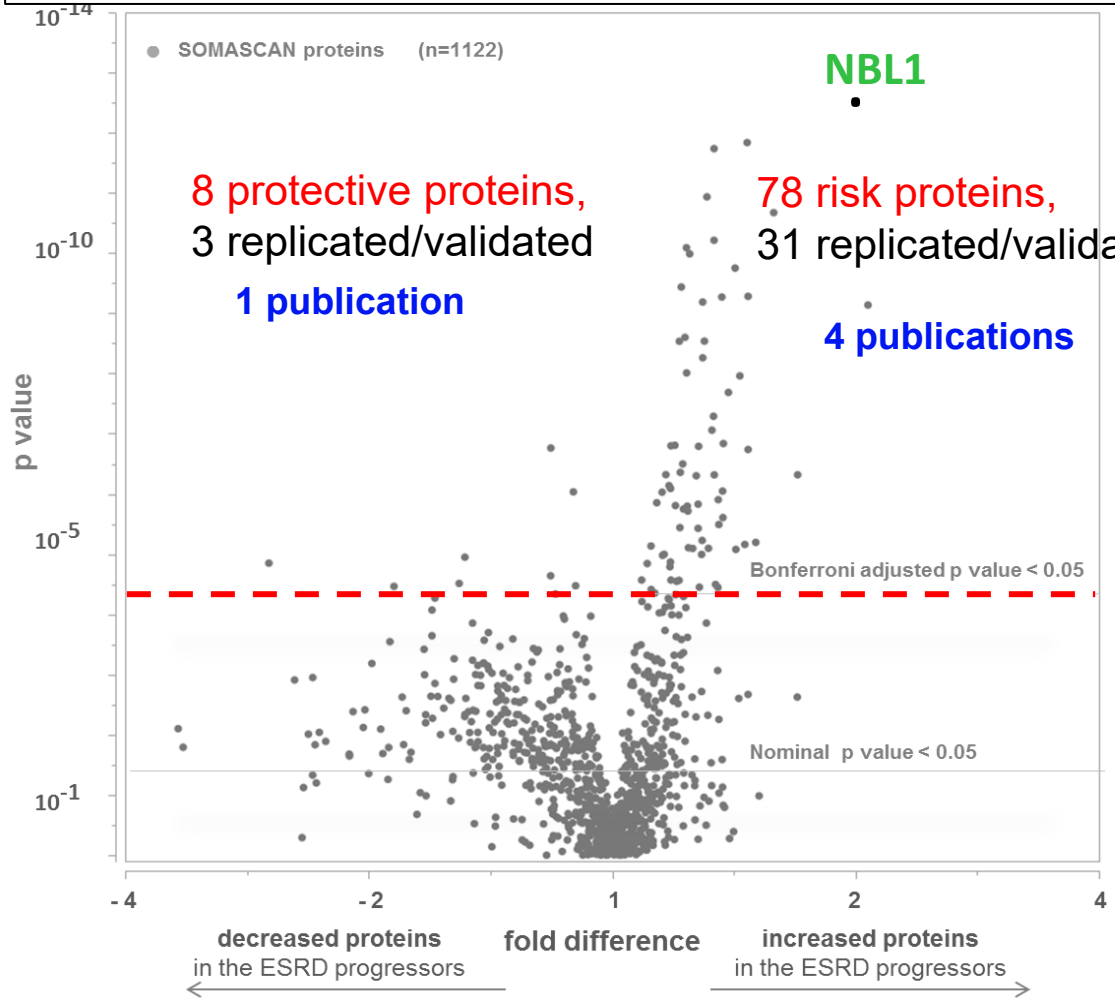
Results of *SOMAscan* screening (n=1129 Proteins) : Plasma proteins are plotted according to fold difference between ESKD cases and controls and p-values

Discovery Cohort



Results were analyzed using candidate pathway approach

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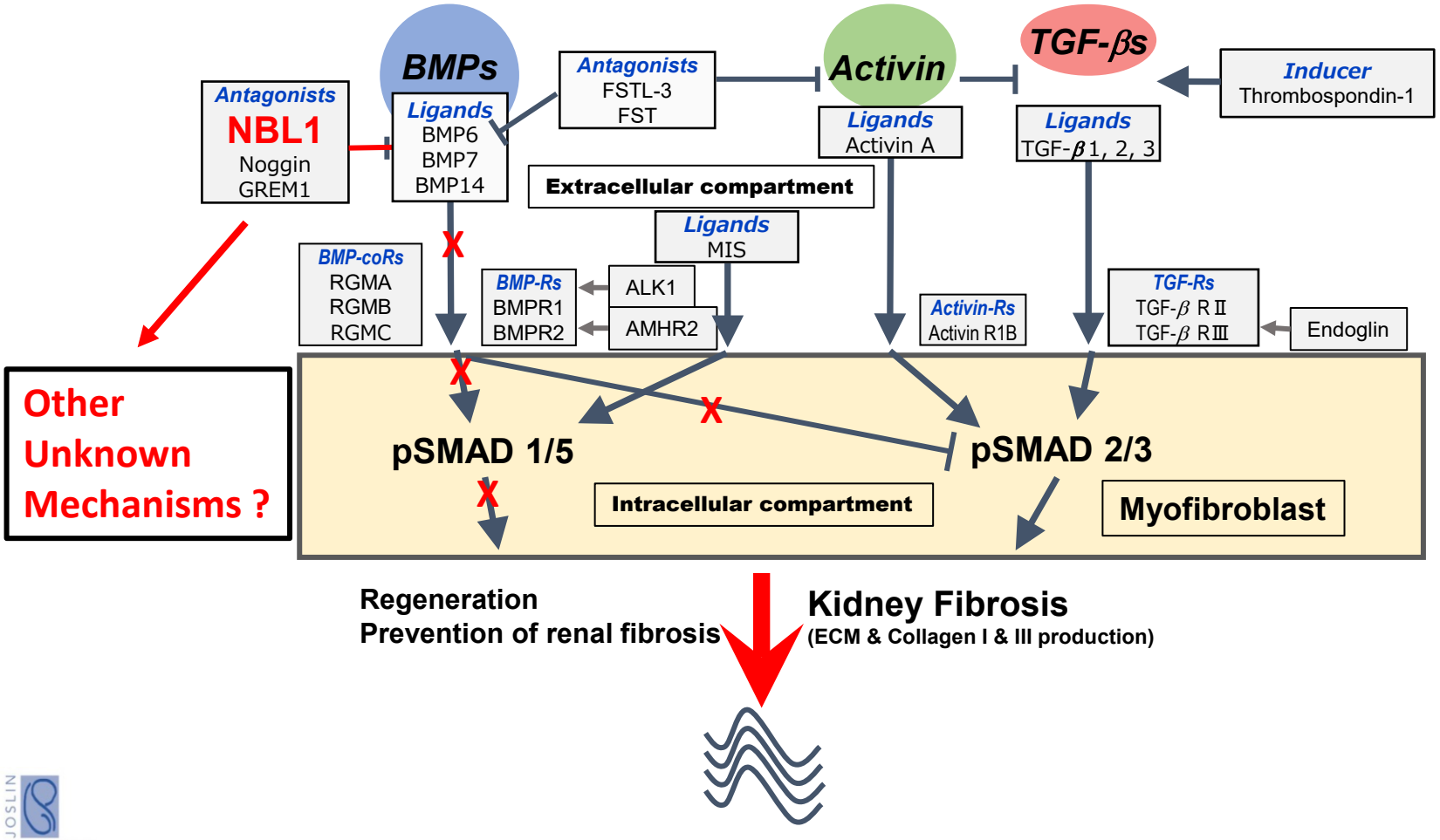
Possible mechanisms through which circulating NBL1 may damage the kidney



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JOSLIN KIDNEY STUDY

The Joslin Kidney Study

Based on Joslin Clinic patients

P.I. Dr. Andrzej S. Krolewski

Aims to investigate determinants and describe the natural history of kidney function decline in type 1 (T1D) and type 2 (T2D) diabetes

- A longitudinal observational study conducted over the last 20 years
- Approximately 5,000 Joslin Clinic patients (half with T1D) are included
- Biobanks of DNA, RNA, plasma, serum and urine were established for all patients
- All patients had lab measurements to determine changes over time
- In albuminuria, kidney function and time of onset of ESKD

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